PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
56491-61226		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE00/01648	28/08/2000	26/08/1999
International Patent Classification (IPC) or national classification and IPC A61K39/395		
Applicant ABSORBER AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/03/2001	26.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Montrone, M Telephone No. +49 89 2399 8711

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SE00/01648

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-45	as originally filed	

Claims, No.:

1-15	with telefax of	26/10/2001

Drawings, sheets:

1/14-14/14	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 15.

because:

   ☒ the said international application, or the said claims Nos. 15 with respect to IA relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-5, 8, 12-15
	No:	Claims 6, 7, 9-11
Inventive step (IS)	Yes:	Claims 1-5, 12-15
	No:	Claims 6-11
Industrial applicability (IA)	Yes:	Claims 1-14
	No:	Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separat sh t

VII. Certain def cts in the international application

The following defects in the form or contents of the international application have been noted:
s e separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
s e separate sheet

Reference is made to the following documents:

D1: Xenotransplantation, vol. 2, 1995, pg.: 295-305
D2: TINS, vol. 14, 1991, pg.: 341-346
D3: Nature Medicine, vol. 1, 1995, pg.: 1189-1194
D4: J. Immunol. Meth., vol. 222, 1999, pg. 31-44

The documents D2 to D4 were not cited in the international search report. Copies of the documents are appended hereto.

Item III:

Claim 15 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(i) PCT).

Item IV:

The requirements of unity of invention (Rule 13 PCT; see further Guidelines C-III,7) are not fulfilled (see invitation to restrict or to pay further fees, dated 17.07.01) .

Since the applicant has paid one further examination fee, the examination with respect to novelty, inventiveness and industrial applicability will refer to the subject-matter of both groups of inventions, namely:

Group I: Claims 1 to 11, 15 and
Group II: Claims 12 to 14

Item V:

1. Claim 1 refers to a transplantation material, characterised in that it has been

produced by (a) dissociation of porcine embryonic or fetal neural tissue, (b) removal of macrophages and/or microglial cells by exposing the preparation of step (a) to antibodies against the Galα1-3Galβ1-R epitope and a complement reagent.

D3 discloses trypsinized porcine embryonic or fetal neural tissue in cell culture which appears to consist solely of neural cells (see abstract and page 1193, left col., third para. to right col. first para.). Claim 1 is considered to be a product by process claim which is only then considered to be novel if the product per se is novel. However, the transplanted cells of D3 were not grown in culture prior to transplantation and thus contained microglial cells. Thus, D3 is no longer considered to be detrimental to the novelty of the subject-matter of claims 1 to 5 (Article 33(2) PCT).

Thus, the transplantation material of claim 1 is considered to be novel and complies with the requirements of Art. 33(2) PCT. The same applies to the subject-matter of claims 2 to 4 dependent thereon, to the use of said material according to claim 5 and the method of treatment according to claim 15. In addition, the subject-matter of claim 8 is considered to be novel. Moreover, the process for removing macrophages and/or microglial cells from porcine embryonic or fetal neural tissue according to claim 12 and claims 13 and 14 dependent thereon are considered to be novel since none of the available prior art documents discloses such a process.

Consequently, the subject-matter of claims 1 to 5, 8, and 12 to 15 is considered to be novel and complies with the requirements of Art. 33(2) PCT.

2. Moreover, the subject-matter of claims 1 to 5 and 12 to 15 appears to be inventive since the specific removal of macrophages and/or microglial cells by antibodies directed against the Galα1-3Galβ1-R epitope in combination with a complement reagent is nowhere taught nor can it be obviously deduced from the teaching of the available prior art documents.

3. However, the subject-matter of claims 6, 7 and 9 to 11 is not considered to be novel for the following reasons:

Claim 6 refers to a kit for use in treating a porcine tissue in order to reduce its immunogenicity, characterised in that it comprises one or more enzymes for tissue dissociation, a preparation of an antibody against the Galα1-3Galβ1-R epitope and a complement reagent.

D4 discloses several methods for the screening of agents and methods for the prevention of hyper acute rejection of pig xenotransplants (see abstract). The method is based on the in vitro culture of different porcine cells in the presence of polyclonal anti-Galα1-3Gal human or baboon sera and complement. If primary aortic endothelial cells were used, then collagenase treatment was carried out before performing the cytotoxicity assay (see page 32, first to third para.; page 33, first to fifth para.). If heat-inactivated serum was used then rabbit complement was separately added (see page 37, second para.). Efficient killing of pig cells by human serum containing complement could be shown (see page 41, second to fourth para.). This means that all the components of the kit of claim 6 are known from D4. The kit of claims 6 to 11 is a product claim referring to a first medical use. Also D4 refers to a medical use. This means that the medical use of said kit claims is not limiting in the present case. Thus, D4 is still considered to be detrimental to the novelty of the subject-matter of claims 6, 7, 9, 10 and 11.

Consequently, the subject-matter of claims 6, 7, 9, 10 and 11 is not considered to be novel and does not comply with the requirements of Article 33(2) PCT.

4. Moreover, the subject-matter of claim 8 appears not to be inventive for the following reasons:

D2 is considered to be the closest prior art. Said document discloses the pretransplant depletion of dendritic and Langerhans cells by antibodies (see D2, page 341, left col., fifth para. to right col., first para.). Moreover, D2 speculates that microglial cells are involved in augmenting neural graft rejection within the CNS (see page 343, left col., first para.). The subject-matter of claim 8 is distinguished therefrom by depleting macrophages and/or microglial cells. This difference results in the specific depletion of immunogenic cells in the CNS.

The objective problem to be solved by the present application was thus to reduce the

immunogenicity of CNS transplants.
The problem was solved by depleting macrophages and/or microglial cells by an antibody. However, D2 already teaches the antibody induced depletion of immunogenic and antigen presenting cells, such as dendritic cells. Moreover, D2 teaches that microglial cells represent the resident tissue macrophages within the CNS. Thus, the person skilled in the art would have combined the teaching of D2 with his general knowledge that macrophages or microglial cells are the antigen presenting cells of the CNS in order to solve the problem mentioned above and would have arrived at the claimed subject-matter falling within the scope of claim 8 without employing any inventive skill. Consequently, the subject-matter of present claim 8 does not appear to be inventive and does not fulfil the requirement of Article 33(3) PCT.

5. For the assessment of the present claim 15 on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Item VI:

The document Eur. J. Neuroscien. Sppl., Vol. 11, 24-28 June 2000 could be relevant to the subject-matter of the present application if the priority of the claims is not valid.

Item VII:

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 to D4 is not mentioned in the description, nor are these documents identified therein.

Item VIII:

1. The scope of claim 6 "for use in treating porcine tissue" is not fully supported by the description, contrary to the requirements of Art. 6 PCT. In particular, D4 teaches that porcine tissue treated with anti-Gal antibodies and complement will be killed. Additionally, the invention cannot be carried out over the whole scope claimed, contrary to the requirements of Article 5 PCT. The applicant filed the document "Cell Transplant. vol., 10, pg. 25 to 30 in order to support the whole scope claimed in present claim 6. However, said document clearly states that only porcine dopaminergic neurons will not be killed by anti-Gal antibodies in combination with complement. The applicant is reminded that the scope of claim 6 is not restricted to these particular cells.